

## **Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in the specification:

### **Listing of Claims**

1. (currently amended) A method to predict which patient will be ~~more~~ likely to develop edema when treated with a drug comprising the steps of:
  - a) determining RNA expression levels in a biological sample for a plurality of the 13 predictor genes shown in Table 2;
  - b) comparing patients gene expression profile to the mean *No Edema* expression profiles shown in Table 3;
  - c) determining the similarity between the two gene expression profiles resulting from the comparison in (b);
  - d) determining the likelihood that the patient will develop edema when treated with a drug by means of the degree of similarity determined in (c).
2. (currently amended) The method of Claim 1, wherein the ~~said~~ similarity determined in (c) is the mathematical correlation coefficient obtained by comparing the said two gene expression profiles.
3. (currently amended) The method of Claim 2, wherein the ~~said~~ correlation coefficient determined in (c) is the Pearson Correlation Coefficient (PCC).
4. (currently amended) The method of Claim 3, wherein step (d) ~~is determined by~~ comprises determining that the patient will be more likely to develop edema than not, when treated with a drug, if the PCC is  $<0.37$  ; and determining that the patient will be more likely not to develop edema than to develop it if the PCC is  $\geq 0.37$ .

5. (currently amended) A method to predict, with high sensitivity, which patients will be more likely to develop edema when treated with a drug, such that no more than 15% of *Edema* cases will be misclassified as having *No Edema*, comprising the steps of:
  - a) determining RNA expression levels in a biological sample for a plurality of the 13 predictor genes shown in Table 2;
  - b) comparing patients gene expression profile to the mean *No Edema* expression profiles shown in Table 3;
  - c) determining the PCC between the two gene expression profiles resulting from the comparison in (b);
  - d) determining that the patient will be more likely to develop edema than not, when treated with a drug, if the PCC is negative and  $<0.78$  ; and
  - e) determining that the patient will be more likely not to develop edema than to develop it if the negative PCC is  $\geq 0.78$ .
6. (currently amended) The method of ~~any one of Claims 1 to 5~~, wherein the biological sample comprises a blood sample.
7. (currently amended) The method of ~~any one of Claims 1 to 6~~, wherein all the 13 predictor genes in Table 2 are used.
8. (currently amended) The method of ~~any one of Claims 1 to 7~~, wherein the drug is a tyrosine kinase inhibitor (TKI).
9. (original) The method of Claim 8, wherein the TKI is Imatinib or GLEEVEC™/GLIVEC®.
10. (currently amended) A method to predict which female patient will be ~~more~~ likely to develop edema when treated with a drug, comprising the steps of:
  - a) determining for the two copies of the IL-1 $\beta$  gene, present in the patient, the identity of the nucleotide pairs at the polymorphic site at position -511 base pairs upstream (at position 1423 of sequence X04500) from the transcriptional start site; and
  - b) determining that the patient will be likely to develop edema if both nucleotide pairs at this site are GC and determining that the patient will not be likely to develop edema if at least one nucleotide pair at this site is AT.
11. (original) The method of Claim 10, wherein the drug is a TKI.

12. (original) The method of Claim 11, wherein the TKI is Imatinib or GLEEVEC™/GLIVEC®.
13. (currently amended) A method to predict which female patient will be ~~more~~ likely to develop edema when treated with a drug, comprising the steps of:
  - a) determining for the two copies of the IL-1 $\beta$  gene, present in the patient, the identity of the nucleotide pairs at the polymorphic site at position -31 base pairs upstream (at position 1903 of sequence X04500) from the transcriptional start site; and
  - b) determining that the patient will be likely to develop edema if both nucleotide pairs at this site are AT and determining that the patient will not be likely to develop edema if at least one nucleotide pair at this site is GC.
14. (original) The method of claim 13, wherein the drug is a TKI.
15. (original) The method of claim 14, wherein the TKI is Imatinib or GLEEVEC™/GLIVEC®.
16. (currently amended) A method to predict which female patient will be ~~more~~ likely to develop edema when treated with a drug, comprising the steps of:
  - a) determination of the level of transcription of the IL-1 $\beta$  gene in a biological sample; and
  - b) determining that the patient would be likely to develop edema when treated with a drug if the level is above a threshold level.
17. (currently amended) A method to predict which female patient will be ~~more~~ likely to develop edema when treated with a drug, comprising the steps of:
  - a) determination of the level of the protein expressed by the IL-1 $\beta$  gene in a biological sample; and
  - b) determining that the patient would be likely to develop edema when treated with a drug if the level is above a threshold level.
18. (currently amended) The method of Claim 16 ~~or 17~~, wherein the drug is a TKI.
19. (original) The method of Claim 18, wherein the TKI is Imatinib or GLEEVEC™/GLIVEC®.

20. (currently amended) A method to predict which patient will be ~~more~~ likely to develop edema when treated with a drug comprising the steps of:
- a) determining the pattern of protein expression in a biological sample for two or more of the protein products of the 13 predictor genes shown in Table 2;
  - b) comparing the pattern of protein expression with the pattern expected for the *Edema* and the *No Edema* expression profile shown in Table 3;
  - c) determining that if the pattern is more similar to the *No Edema* pattern that the patient will not be likely to develop edema when treated with a drug; and
  - d) determining that if the pattern is more similar to the *Edema* pattern that the patient will be likely to develop edema when treated with a drug.
21. (original) The method of Claim 20, wherein the protein expression of a plurality of the 13 predictor genes shown in Table 2 is determined.
22. (original) The method of Claim 21, wherein the protein expression of all the 13 predictor genes shown in Table 2 is determined.
23. (currently amended) The method of ~~any one of Claims 20 to 22~~, wherein the drug is a TKI.
24. (original) The method of Claim 23, wherein the TKI is Imatinib or GLEEVEC™/GLIVEC®.
25. (canceled).
26. (currently amended) A method to design clinical trials for the testing of drugs comprising the steps of:
- a) determining by the use of either ~~the~~ expression profiling or ~~the~~ genotyping methods ~~described above~~ the likelihood that a particular patient will develop edema when exposed to the test drug; and
  - b) assigning that patient to the appropriate classification in the clinical ~~study~~ trial based on the results of the determination in (a).
- (claims 27-42 canceled).

43. (currently amended) A kit for predicting which patient will be ~~more~~ likely to develop edema when treated with a drug comprising:
- (a) a means for determining the pattern of protein expression corresponding to the two or more of the 13 predictor genes shown in Table 2;
  - (b) a container suitable for containing the ~~said~~ means and the biological sample of the patient comprising the proteins, wherein the means can form complexes with the proteins;
  - (c) a means to detect the complexes of (b); and ~~optionally~~
  - (d) instructions for use and interpretation of the kit results.
44. (canceled).
45. (currently amended) A kit for predicting which patient will be ~~more~~ likely to develop edema when treated with a drug comprising:
- (a) a means for determining the level of the protein expressed by the IL-1 $\beta$  gene;
  - (b) a container suitable for containing the ~~said~~ means and the biological sample of the patient comprising the protein, wherein the means can form complexes with the protein;
  - (c) a means to detect the complexes of (b); and ~~optionally~~
  - (d) instructions for use and interpretation of the kit results.
46. (currently amended) The method of ~~any one of Claims 17 to 19~~, wherein the determination step (a) further comprises the use of a kit of ~~any one of Claims 37 to 42, or 45~~.
47. (currently amended) The method of ~~any one of Claims 20 to 24~~, wherein the determination step (a) further comprises the use of a kit of ~~any one of Claims 34 to 36, or 38 to 44~~.

(claims 48-71 canceled).

72. (original) A kit for determining the identity of the nucleotide pair at the -511 position of the IL-1 $\beta$  gene (at position 1423 of sequence X04500) from the transcriptional start site for the two copies of the IL-1 $\beta$  gene present in the patient; comprising:
- a) a container comprising at least one reagent specific for detecting the nature of the nucleotide pair at the at the -511 position of the IL-1 $\beta$  gene (at position 1423 of sequence X04500) from the transcriptional start site for the two copies of the IL-1 $\beta$  gene present in the patient; and
  - b) instructions for interpreting the results based on the nature of the said nucleotide pair.
73. (original) A kit for determining the identity of the nucleotide pair at the polymorphic site at position -31 base pairs upstream (at position 1903 of sequence X04500) from the transcriptional start site; comprising:
- a) a container comprising at least one reagent specific for detecting the nature of the nucleotide pairs at the polymorphic site at position -31 base pairs upstream (at position 1903 of sequence X04500) from the transcriptional start site; and
  - b) instructions for interpreting the results based on the nature of the said nucleotide pair.

(claims 74-75 canceled).